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Crucial progress in understanding Fragile X mental retardation protein

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Researchers in the Department of Obstetrics, Gynecology & Reproductive Sciences at Yale School of Medicine have identified a new regulatory target for the Fragile X mental retardation protein (FMRP), laying the groundwork for possible new treatments for Fragile X syndrome(FXS), the leading inherited form of mental retardation.

The findings, published in the early online edition of the June Proceedings of the National Academy of Sciences, also have implications for autism, which shares a common physiological pathway with FXS.

Fragile X syndrome is mainly caused by a mutation in the FMR1 gene on the X chromosome, leading to the loss of FMRP, which is abundantly expressed in the brain and testes. Without this protein, brain development is hampered and nerve cells cannot communicate with each other appropriately, resulting in the reduced ability to learn and memorize. Fragile X syndrome affects about one in 4,000 males and one in 8,000 females. About 20 percent of children with FXS have autism and about five percent of autistic children have FXS.

The research team led by Yingqun Huang, M.D., assistant professor in Yale Ob/Gyn, previously found that FMRP interacts with a nuclear mRNA export protein NXF2, in the mouse brain and testes. In this study, the team used mouse neuronal cells to explore the functional characteristics of this interaction.

“We found that FMRP, together with NXF2, acts to down-regulate the expression of its target, the messenger RNA that encodes NXF1, which is an essential protein needed to transport most mRNAs from the nucleus to the cytoplasm of cells,” said Huang. “Our findings explain why the NXF1 protein level is much lower in the hippocampal neurons involved in learning and memory than in many other cells. This may suggest that a high level of NXF1 might hinder the function of these cells.”

“We are one of the first two labs to show that FMRP regulates gene expression at the mRNA stability level,” Huang added. “The idea is to find the mechanisms underlying the function of FMRP so in the future, we can develop more effective interventions.”

Huang said future studies will look more closely at how FMRP works with NXF2 to regulate its targets. She said, “We expect to identify more targets which are regulated by FMRP and NXF2. This will be a new direction in the FMRP research field.”

Source: Yale University